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10/547,066	05/22/2006	Marianne Bruggemann	M0106.70004US00	4387

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	PAPER NUMBER
1633	
MAIL DATE	DELIVERY MODE
09/15/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/547,066	BRUGGEMANN, MARIANNE	
	Examiner	Art Unit	
	Q. JANICE LI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-73* is/are pending in the application.

4a) Of the above claim(s) *9, 10, 13, 15-17, 19, 22-38, 41-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11,12,14-16,18,20,21,39 and 40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 August 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment and response filed 6/11/09 are acknowledged. Claim 15 has been amended. Claims 1-8, 11, 12, 14-16, 18, 20, 21, 39, 40 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims and persuasive argument will not be reiterated. The arguments in 6/11/09 response would be addressed to the extent that they apply to current rejection.

Election/Restrictions

Applicant's election of Group I and species election, drawn to a non-human mammal having all endogenous IgH VDJ segments, are acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-8, 11, 12, 14-16, 18, 20, 21, 39, 40 read on the elected invention. It is noted claim 22 was inadvertently included in the group I, which should belong to group II. Accordingly, Claims 9, 10, 13, 15-17, 19, 22-38, 41-73 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Election was made **without** traverse in the 9/23/08 response.

Claims 1-8, 11, 12, 14-16, 18, 20, 21, 39, 40 are under current examination.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-6, 8, 11, 12, 14-16, 18, 20, 21, 39, 40 stand rejected under 35 U.S.C. 102(e) as being anticipated by or in the alternative under 35 U.S.C. 103(a) as being obvious over *Rajewsky et al.* (USP 6,570,061, IDS), for reasons of record and following.

Rajewsky discloses transgenic mice whose genome comprising targeted gene replacement of the mouse heavy chain immunoglobulin constant region genes with the human IgH constant region gene (e.g. see the abstract and claims 1-3). Hence the genome of these genetically modified mice does not contain a nucleic acid encoding an endogenous IgH constant region locus polypeptide, but contains all the IgH variable region, D and J segments. *Rajewsky* further teaches the mice were obtained either through conventional gene targeting or by use of the Cre-loxP recombinant system. In working examples, a targeting vector contains an IgL C gene enhancer sequence (MCκ) and a selectable marker neomycin gene was disclosed (e.g. column 8, lines 45-64). *Rajewsky* also teaches breeding the transgenic mice to produce progenies (e.g. col 7, lines 34-44). Accordingly, *Rajewsky* anticipated instant claims.

It appears that the C region gene replacement claimed by *Rajewsky* embraces both a total or a partial replacement, wherein in the working examples, only one portion of the C region was replaced (Cγ1), such as indicated in claims 7 and 8, wherein the mouse contains some of the endogenous IgH-C. However, given the levels of the skilled as established by *Rajewsky*, one would have known how to make a mouse having total depletion of the endogenous IgH-C gene if one desires to do so.

Thus, the claimed invention as a whole was at least *prima facie* obvious, if not anticipated, by the reference, in the absence of sufficient, clear and convincing evidence to the contrary.

In the remarks, the applicant argues that *Rajewsky* focus on replacement of an endogenous gene with a human gene, does not disclose genetically modified mice lacking *any* IgH C region.

The argument has been fully considered. It is noted instantly rejected claims are not limited to lacking any IgH-C region, they embrace mice having partial endogenous IgH C region and/or having a human replacement IgH C region. Accordingly, the rejection still applies to these claims.

Claim Rejections - 35 USC § 103

Claims 1 and 7 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Rajewsky et al.* (USP 6,570,061) in view of *Fell et al.* (USP 5,202,238), for reasons of record and *supra*.

The teaching of *Rajewsky* is discussed in detail *supra*, which teaches using a light chain enhancer but not an IgH C gene enhancer sequence in a targeting vector for making a genetically modified mouse.

Fell supplemented the deficiency by establishing it was well known in the art that an IgH C gene enhancer sequence may be used in a targeting vector. *Fell* teaches replacing the Ig heavy chain constant region of a mouse with that of human, and constructs a plasmid vector which contains the constant region exons of human IgG1 (Cg1) flanked by the murine heavy chain enhancer (MHE), and the neomycin resistance gene (NEO) (column 7, lines 40-45, FIGs. 4, 7).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the targeting vector as taught by *Rajewsky et al,* by simply substituting the enhancer with the one as taught by *Fell, Jr. et al* with a reasonable expectation of success. Given the knowledge of the skilled in the art, this limitation falls within the bound of optimization. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 11, 12, 14-16, 18, 20, 21, 39, 40 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a genetically modified *mouse* lacking endogenous IgH constant region and containing the endogenous IgH VDJ region, does not reasonably provide enablement for making any non-human *mammal* having the recited features and it does not reasonably provide enablement for how to use the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims, for reasons of record and following.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the scope of the claims relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

Given the broadest reasonable interpretation, the claims embrace any and all non-human animals lacking endogenous IgH constant region and containing the endogenous IgH VDJ region.

In view of the teaching of the specification, it reduces to produce two genetically modified mouse whose genome comprising a deletion of IgH constant gene (CΔ), wherein such deletion was lost in the second generation (see table 1, page 38), and hence, the specification fails to produce any progeny of the (CΔ) mice. The specification teaches making a targeting construct containing loxP sites, making ES cell clones with

targeting events, microinjecting the ES cells into Balb/c blastocysts, and transplanting such blastocysts to foster mothers. Subsequently, the mice were crossed with Cre mice to generate (CΔ) mice (example 6). The specification also teaches the process for producing the (CΔ) mice was highly inefficient (e.g. examples 7 & 9) and the removal of all C-genes led to a complete disappearance of immature and mature B-cells expressing IgH- and L-chain and silences the IgH locus at the transcriptional level, no detectable levels of antibody produced in the (CΔ) mice (see e.g. Specification, page 42-45). The specification fails to produce any non-human mammal beyond the mouse.

The specification provides a general method of producing the claimed non-human animal (e.g. pages 19-20), which requires the use of a non-human mammal embryonic stem cell (step a). However, the state of the art is such that ES cell technology is generally limited to the mouse system at present, and that only "putative" ES cells exist for other species (see Moreadith *et al.*, **J. Mol. Med.**, 1997, Vol. 75 p. 214, *Summary*). Note that "putative" ES cells lack a demonstration of the cell to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. Such a demonstration has not been provided by the specification or the prior art with regard to the generation of any species of animal ES cells, other than the mouse, which can give rise to the germline tissue of a developing animal. As the claims are drawn to methods involving the manipulation of animal embryonic stem (ES), and particularly since the subject matter of the specification and the claimed invention encompasses the use of such cells for the generation of a transgenic animal, the state of the art supports that only **mouse ES cells** were available for use for production of transgenic/gene knockout mice.

This is further supported by Pera *et al.* [**Journal of Cell Science** 113: 5-10 (2000)] who present the generic criteria for pluripotent ES or EG cells [see p. 6, 2nd column] and state that, "THUS FAR, ONLY MOUSE EG OR ES CELLS MEET THESE GENERIC CRITERIA. PRIMATE ES CELLS MEET THE FIRST THREE OF THE FOUR CRITERIA, BUT NOT THE LAST. NUMEROUS OTHER CANDIDATE MAMMALIAN ES CELLS HAVE BEEN DESCRIBED OVER THE YEARS IN DOMESTIC AND LABORATORY SPECIES, BUT ONLY IN THE MOUSE HAVE ALL CRITERIA BEEN MET RIGOROUSLY." [See p. 6, 2nd column, last paragraph]. *Kuroiwa et al* (Nature Genetics 2004;36:775-80) teach the ES cells suitable for gene targeting are not available for species other than mouse. In view of such, the claimed invention does not appear to be enabled for any non-human mammals in the absence of clarification of the contradictory evidence found in the references.

As to how to use the claimed non-human mammals, the specification teaches it is desirable in order to produce antibodies of a foreign origin, expressed from introduced genes. However, since the (CΔ) mice disclosed in the specification had a complete disappearance of immature and mature B-cells expressing IgH- and L-chain and silences the IgH locus at the transcriptional level, it was unclear and the specification fails to teach whether the B-cells would reappear upon introducing Ig genes of foreign origin, and accordingly, the specification fails to provide an enabling disclosure concerning how to use the claimed invention.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

In the remarks, the applicant first argues Table I of the specification does show that four mice in the second generation had a locus deletion.

In response, it is noted the title of Table 4 is "Transmission rate of Homologous integration and locus deletion". However, the referred four mice in the row that shows locus deletion do not have homologous integration. The table is unclear as to what kind of locus deletion occurred in the four mice since the deletion does NOT appear to be the consequence of a homologous integration targeting event according to the description in the table.

As to how to use the claimed non-human mammals, in response to the question that the (CΔ) mice disclosed in the specification had a complete disappearance of immature and mature B-cells expressing IgH- and L-chain and silences the IgH locus at the transcriptional level, the applicant cited a document by Bruggemann as evidence of a reversible B cell development. However, the cited document is not enclosed as indicated and is not currently on record, and hence the evidence can not be reasonably evaluated.

As to the availability of mammalian cells other than the mouse, the applicant argues that the cited art are dated before instant filing date.

In response, the Office is not aware of any advance in the art concerning the availability of mammalian ES cells other than mouse as of today, which is the starting material for making instantly claimed mouse and the applicant fails to provide any

evidence establishing that such state of the art has changed at the time of instant filing date to the point that ES cells for other mammalian species had become available. Thus, the instant disclosure fails to provide an enabling disclosure commensurate with the scope of the claims in the absence of clear and convincing evidence to the contrary.

The applicant also argues that *Kuroiwa et al*. teaches that gene targeting and gremlin transmission can be achieved without the use of ES cells.

In response, the instant specification is completely silent and thus fails to teach gene targeting in the absence of ES cells for other species of mammalian animals in the context of making the claimed mammals. For example, the availability of the genus Immunoglobulin genes concerning the genus of mammals, the availability of targeting tools for the genus, the similarity/differences of B cell development between mouse and other mammals, the rate of germline transmission in these mammals, etc. Accordingly, the skilled in the art intend to practice the invention has to carry out undue experimentation to figure out how to make and use the mammals as claimed by themselves. Accordingly, the specification fails to provide an enabling disclosure commensurate with the scope of the claims.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. JANICE LI** whose telephone number is **571-272-0730**. The examiner can normally be reached on 9 AM -7:00pm, Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at **800-786-9199**.

/Q. JANICE LI, M.D./
Primary Examiner, Art Unit 1633